Huntington's Chorea in Michigan[1,2]

I. Demography and Genetics

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with the collaboration of

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INTRODUCTION

AMONG THE RARE DOMINANT TRAITS of man, Huntington's chorea has enjoyed a certain notoriety ever since the well-known description of the disease by George Huntington in 1872. The striking and serious nature of the disease, including mental and emotional impairment as well as chorea, together with its dominant heredity, has attracted many investigators. The first recognition of the disease as a distinct entity may have been made by the Norwegian J. C. Lund in 1860 (cf. Ørbeck and Quelprud, 1954) but general knowledge of the disease only followed Huntington's paper in 1872. Among the most important genetic studies of this trait are those by Panse (1942), who made a study of the clinical, social, and genetic aspects of Huntington's chorea in the Rhineland, and by Bell (1934) and Sjögren (1935) who made critical studies of its formal genetics in material from the literature and from Swedish communities, respectively. Surveys of the frequency and distribution of the disease have now been made for several large areas, as will be summarized below. The many smaller studies will not be reviewed here.

The increased interest in the population genetics of man, particularly in natural selection and mutation, has focused attention on several ways in which Huntington's chorea appears to differ from most rare dominant traits. Family studies revealed that, in contrast to dominant traits such as for example, achondroplasia (Mørch, 1941) and neurofibromatosis (Crowe, *et al.*, 1955), propositi for Huntington's chorea almost invariably have a parent affected with Huntington's chorea if both parents were long-lived. The mutation rate therefore appears to be quite low. This finding

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agrees well with the high fertility of choreics (here and throughout this paper "choreic" refers only to Huntington's chorea), relative to their non-choreic sibs, found in several studies. In fact, the extensive study of Panse (1942) and the study of a single large family group by S. C. Reed and Palm (1951) both found choreics to be more fertile than their apparently normal sibs. If this were in fact the case, and there are a number of reservations which will be considered later, it would be of the greatest interest in human genetics. It would be an instance of a rare dominant gene in the process of replacing its "normal" allele. This process, postulated as part of the evolution of all organisms, has yet to be clearly demonstrated in man. [Neel (1957) has suggested that such a process may now be observable in Africa among the genes responsible for certain hemoglobin variants.] The unsatisfactory nature of the hypotheses needed to account for the present rarity of Huntington's chorea and the difficulty in imagining a population composed largely or solely of choreics add to the interest of this situation. The present investigation was undertaken as an attempt to elucidate this problem in population genetics, as well as to obtain other data, demographic and clinical, on Huntington's chorea in Michigan. A brief report of some of the results of this study has already been given (Reed, 1957).

METHOD OF STUDY

An attempt was made to obtain data on all persons known, or reliably reported, to have Huntington's chorea who have ever lived in the Lower Peninsula of Michigan (having 93.8 per cent of the total population of the state in 1940). For the purposes of the present study attention was primarily restricted to those kindreds (groups of biologically related individuals) having at least one medically diagnosed choreic living in the Lower Peninsula on April 1, 1940. This procedure was adopted for several reasons. One purpose of the study is to obtain frequency estimates and to make comparisons with U. S. Census data. Choreics usually do not come to medical attention for several years after onset of the disease, sometimes not for ten or more years. To be reasonably complete, a census of Huntington's chorea must be for some appropriate past date. April 1, 1940 was chosen as being suitable for completeness and also for coinciding with the U. S. Census of that year. Restricting the study to this date also has the advantage of making the data more homogeneous in time, an important consideration for certain variables of interest, e.g. fertility. For a few purposes only, such as the study of possible mutation, all available kindreds were utilized, and for other purposes, involving comparison within sibships, four sibships from the Upper Peninsula of Michigan, including five choreic members on April 1, 1940, were included.

Depending on the variable studied, data were available on choreics alone, choreics and their normal sibs, or choreics, normal sibs, and the population of Michigan as a whole. Comparison of choreics with the general population, as well as with normal sibs, should give valuable information not previously available.

This first part of the study will be concerned with the demography, social characteristics, and genetics of Huntington's chorea, while the second part will cover relative fitness and mutation. Clinical aspects of Huntington's chorea are not considered in this study but will be presented elsewhere.

ASCERTAINMENT AND EVALUATION OF THE DATA

The medically-diagnosed propositi of the kindred were obtained from several sources. Two trained field-workers, familiar with the disease, in 1954 and 1955 reviewed the diagnosis files of all State Hospitals (for mental patients) in Michigan and compiled a list of persons living or dead, with firm or possible diagnoses of Huntington's chorea. This list was deliberately made very inclusive so as to include unrecognized cases. The files of the Veterans Administration hospitals in Detroit and Battle Creek were also reviewed. Lists of all choreics seen in University Hospital of the University of Michigan, and Wayne County General Hospital (which serves Detroit largely), and a number of County Infirmaries were also obtained. Kindreds already on file in the Heredity Clinic, University of Michigan, were incorporated into the study. The variety of ways in which individuals were ascertained is illustrated in table 1. It may be noted that about one-third of the choreics living in 1940 were ascertained only through affected relatives, being unknown to official sources, while a little more than a third were ascertained through two or more independent sources.

The Michigan relatives of the new cases of definite or possible Huntington's chorea were contacted by one of the field workers and a detailed family history was obtained. When relatives were reported to have symptoms of chorea, whether in Michigan or not, these reports were checked as far as possible, by correspondence with relatives and hospitals if out of the state or, if in Michigan, by home visits and contacts with physicians and hospitals. Death certificates were obtained, when other information was inadequate, and were frequently of value. This follow-up

TABLE 1. METHOD OF ASCERTAINMENT OF WHITE CHOREICS RESIDENT IN THE LOWER PENINSULA OF MICHIGAN ON APRIL 1, 1940

Sex	Ever Institutionalized*	Mode of Ascertainment							
		1	2	3	4	5	6	7	Total
Male	Yes	1	4	20	0	0	23	6	54
	No	1	21	0	3	1	3	1	30
	Total	2	25	20	3	1	26	7	84
Female	Yes	0	2	26	0	0	38	9	75
	No	5	30	0	3	1	1	1	41
	Total	5	32	26	3	1	39	10	116
Total	Yes	1	6	46	0	0	61	15	129
	No	6	51	0	6	2	4	2	71
	Total	7	57	46	6	2	65	17	200

* As of 1956.

† 1: Only through a son or daughter.
2: Only through a choreic relative other than son or daughter.
3: Only through a mental institution (not County Infirmaries).
4: Only through University Hospital, Ann Arbor.
5: Only through other medical or social agencies.
6: Through any choreic relative *and* other sources.
7: Through two or more medical or social sources, not through choreic relatives.

procedure was carried out on each kindred, whether or not it appeared to contain a Michigan choreic living on April 1, 1940. A number of persons who had not been medically examined were examined at home or in University Hospital by one of us (J. H. C.) and a diagnosis of Huntington's chorea was made or excluded. After all indicated fieldwork, examinations, and correspondence had been completed, each kindred was reviewed for compatibility with a diagnosis of Huntington's chorea. Only those kindreds having one or more persons with a firm diagnosis were retained in the study. A number were removed because of inadequate diagnostic information. A supporting family history of chorea was not required for acceptance, but in the majority of kindreds this was present.

RESULTS

Race, sex, and age composition of the sample

The results to be given here are for the Lower Peninsula of Michigan for April 1, 1940 as described above. Two hundred and three individuals, either medically diagnosed or reliably reported to be choreic by lay sources (and having a close relative who is medically diagnosed) were ascertained. They were in 164 sibships which were in 124 kindreds. Three of these persons, in two sibships in separate kindreds, are of Negro ancestry; the others are of Caucasian ancestry. These 203 persons are divided between 85 males and 118 females. Of the 200 whites, 47 (23.5%) were in mental institutions on April 1, 1940. The above facts are presented in table 2 which gives distribution by age, sex, race, and institutional status. (In this and other tables the values for the mean, standard deviation, and standard error are computed from ungrouped data.)

In table 3 the choreic and diagnostic status on April 1, 1940 of members of sibships containing one or more persons with Huntington's chorea (according to medical

TABLE 2. AGE DISTRIBUTION OF WHITE* CHOREICS ON APRIL 1, 1940 IN THE LOWER PENINSULA OF MICHIGAN BY SEX AND INSTITUTIONAL STATUS

Sex	In Mental Institution	Age on April 1, 1940												No.	Mean	Standard Deviation	Standard Error
		15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79				
Male	Yes	0	0	1	1	1	4	2	2	3	1	4	1	0	20	52.35	12.86	2.88
	No	2	1	2	6	7	8	14	9	7	6	2	0	0	64	45.77	11.61	1.45
	Total	2	1	3	7	8	12	16	11	10	7	6	1	0	84	47.33	12.17	1.33
Female	Yes	0	0	0	0	1	5	7	3	4	4	2	0	1	27	52.59	9.84	1.89
	No	1	0	4	10	9	14	7	15	11	10	2	5	1	89	48.29	12.58	1.33
	Total	1	0	4	10	10	19	14	18	15	14	4	5	2	116	49.29	12.10	1.12
Total	Yes	0	0	1	1	2	9	9	5	7	5	6	1	1	47	52.49	11.10	1.62
	No	3	1	6	16	16	22	21	24	18	16	4	5	1	153	47.24	12.21	0.99
	Total	3	1	7	17	18	31	30	29	25	21	10	6	2	200	48.47	12.14	0.86

* Three Negro choreics were ascertained. Their status on April 1, 1940 was as follows: (1) Female, age 28, not institutionalized; (2) Female, age 29, institutionalized; (3) Male, age 51, institutionalized.

TABLE 3. STATUS OF MEMBERS OF SIBSHIPS CONTAINING ONE OR MORE CHOREICS ON APRIL 1, 1940. ONLY SIBSHIP MEMBERS LIVING IN THE LOWER PENINSULA OF MICHIGAN

Sex	Race	Choreic Status on April 1, 1940 and at Time of Last Investigation																Total
		1	1.5		2		3			4			5			6			
			A	B	A	B	A	B	C	A	B	C	A	B	C	A	B	C	
Male	White	22	1	0	61	47	3	1	0	100	8	1	0	0	0	8	2	2	195
	Negro	1	0	0	0	0	1	1	0	0	0	0	0	0	0	3	0	0	5
Female	White	25	3	3	88	65	0	0	0	114	13	4	2	0	0	2	1	1	234
	Negro	1	0	0	1	1	0	0	0	0	0	0	0	0	0	1	0	0	3
Total	White	47	4	3	149	112	3	1	0	214	21	5	2	0	0	10	3	3	429
	Negro	2	0	0	1	1	1	1	0	0	0	0	0	0	0	4	0	0	8

Status code: 1. Huntington's chorea diagnosed medically.
1.5 "Chorea" or ? Huntington's chorea diagnosed medically.
2. Huntington's chorea reported by reliable lay observers with no contradictions.
3. Huntington's chorea according to dubious or contradictory reports.
4. No Huntington's chorea according to lay report.
5. No Huntington's chorea according to medical report.
6. No information.
A = Status on April 1, 1940.
B = Number in A medically diagnosed between April 1, 1940 and June, 1956.
C = Number in A in status "2" at death or by June, 1956.

diagnosis or reliable, uncontradicted, lay report) is presented. (All lay reports were evaluated only with respect to choreiform movements.) Of the 203 white and Negro choreics, 49 had been medically diagnosed by April 1, 1940. Of the remaining 154 persons who are considered to have Huntington's chorea on that data (i.e. statuses 1.5 and 2 in table 3), 115 were medically diagnosed some time after April 1, 1940 but before June 1956. Two of the four dubiously choreic sibs (status 3, not counted as being choreic) developed definite Huntington's chorea at a later late, while 26 of the 216 non-choreic sibs (statuses 4 and 5) also later developed Huntington's chorea. It is thus possible to obtain some idea of the number of adults with the gene for Huntington's chorea who had not developed the disease by 1940. An estimate of the gene frequency will be presented later.

The 203 choreic individuals were ascertained from a population of 4,932,562 (Lower Peninsula of Michigan, 1940 U. S. Census), so that the observed frequency of choreics is 4.12×10^{-5} or about one choreic per 24,000 individuals. This is within the frequency range reported in other studies of populations of European ancestry, as shown in table 4, but, as indicated, none of these studies is exactly comparable to the present investigation. It does appear that the frequency in various populations of European origin (95.7 per cent of the Lower Peninsula is of European ancestry) is quite constant. In contrast to this "European" frequency range of $3.2\text{–}6.5 \times 10^{-5}$, the study of Kishimoto *et al.* (in press) in Japan (Aichi Prefecture, population 3,916,922) found a frequency of 3.22×10^{-6} (13 choreics). Since some 3,000 physicians in this prefecture are said to have been contacted regarding the possible

TABLE 4. FREQUENCY OF INDIVIDUALS WITH HUNTINGTON'S CHOREA IN CERTAIN AREAS*

Area Studied	Date of Census	Population of Area	Number of Choreics			Frequency of Choreics	Investigator	Remarks
			Male	Female	Total			
Rhineland, Germany	1933	7,690,266	—	—	248	3.22×10^{-5}	Panse (1942)	Retrospective frequency. Positive family history apparently required for each choreic
Northamptonshire, England	1955	263,000	5	12	17	6.5×10^{-5}	Pleydell (1954, 1955, 1957)	Not retrospective frequency
Minnesota, U. S. A.	1955	3,174,000 (estimated for 1955)	66	51	117	3.69×10^{-5}‡	Pearson *et al.* (1955) Pearson (1957)	Not retrospective frequency
Aichi Prefecture, Japan	1957	3,916,922	6	7	13	3.32×10^{-6}	Kishimoto *et al.* (in press)	Not retrospective frequency
Lower Peninsula of Michigan, U. S. A.	1940	4,932,562	85	118	203†	4.12×10^{-5}	Present study	Retrospective frequency

* A number of surveys are omitted because an intensive search for non-institutionalized choreics was not made.

† Includes 3 Negroes.

‡ 117/3,174,000. By estimating the number of choreics missed because of migration, Pearson *et al.* (1955) estimate the frequency of choreics in Minnesota to be 5.43×10^{-5}.

existence of Huntington's chorea among their patients, this low frequency may represent a real racial difference in frequency and not an example of under-reporting. If so, this difference raises interesting questions in population genetics concerning the relation of gene frequency and relative fitness in Japan and in the West. These subjects are considered further in the second part of this study.

The proportion of Negroes in Michigan in 1940 was 0.0422, while the observed proportion among the choreics is 0.0148. If the age-specific frequency of the trait is equally common in the two races, 8.314 Negro choreics would be expected. The observed number, three, does not differ significantly from this.

The sex distribution of the 203 choreics, 85 males and 118 females, can be shown to differ significantly from expectation. If the age-specific incidence of Huntington's chorea is equal in males and females, the expected number of choreic males is 106.058 (1940 U. S. Census age and sex data). The probability of deviations as great or greater than that observed is 0.004. The only other survey of a large area for which a sex distribution is given, that of Pearson *et al.* (1955) and Pearson (1957), reveals no deficiency of males, there being 66 males and 51 females. It is not clear why this deficiency of males in the present data should exist, especially since, as discussed

later, there appears to be no deficiency within sibships when considered as of the time of last investigation (i.e. using the status of each sibship member at time of death or as of June 1956). In the course of the study the impression was gained that there was a noticeably greater mobility of males, relative to females, in the early stages of the disease. If so this could lead to under-reporting during this period. The age distribution of table 2, however, does not give weight to this impression. On the other hand, the difference is not due to a sex difference in the mean duration of the disease (table 19).

Demographic and social characteristics

It is of interest to record the earliest known "origins" of the gene for Huntington's chorea present in the 124 kindreds of the Lower Peninsula in 1940. Some previous American studies (Davenport and Muncey, 1916; Vessie, 1932) have emphasized southeastern England as the area from which the choreic ancestors of American choreics came, although these authors recognize that other areas also contributed. The "origins" for the 124 kindreds in the Lower Peninsula are tabulated in table 5. Fifty-one kindreds could be traced outside of the United States; Canada, Germany, and England were the leading areas with 12, 11, and 7 kindreds, respectively. Fifty-two of 73 "American" kindreds were traced outside of Michigan, with New York leading by far with 19 kindreds. Without making a detailed investigation, it appears these "origins" are reasonably consistent with the patterns of immigration to the United States and the migrations leading to the present Michigan population.

The distribution of birthplaces of the white choreics living in 1940, listed in table 6, gives a more recent picture of migration. Twenty-seven (13.5%) of the choreics

TABLE 5. STATE (U. S. A.) OR FOREIGN COUNTRY OF ORIGIN OF EARLIEST TRACEABLE CHOREIC MEMBER OF 124 CHOREIC KINDREDS (LOWER PENINSULA OF MICHIGAN, 1940)

United States		Foreign Country	
State	Number	Country	Number
Michigan	21	Canada	12
New York	19	Germany	11
Indiana	7	England	7
Pennsylvania	7	Poland	4
Ohio	4	Ireland	3
Tennessee	3	Scotland	3
Illinois	2	Italy	2
Alabama	2	Netherlands	2
Arkansas	1	Austria	1
Connecticut	1	Czechoslovakia	1
Iowa	1	Finland	1
Kentucky	1	Greece	1
Maryland	1	Hungary	1
Massachusetts	1	Spain	1
Vermont	1	Yugoslavia	1
"New England"	1		
Total	73	Total	51

TABLE 6. PLACE OF BIRTH OF 200 WHITE CHOREICS LIVING IN THE LOWER PENINSULA OF MICHIGAN ON APRIL 1, 1940

State (U.S.A.) or Country of Birth	Male	Female	Total
Michigan	61	80	141
Indiana	2	5	7
Illinois	0	6	6
Ohio	1	2	3
New York	0	2	2
Other states	4	9	13
Uncertain	1	0	1
Total U. S. A.	69	104	173
Canada	6	5	11
Germany	1	3	4
Scotland	1	2	3
England	1	1	2
Austria	1	0	1
Czechoslovakia	1	0	1
Greece	1	0	1
Hungary	1	0	1
Netherlands	0	1	1
Poland	1	0	1
Spain	1	0	1
Total Foreign	15	12	27

were born outside of the United States, compared to 13.2 per cent in the whole population of the Lower Peninsula. Taking into consideration sex and difference in age composition between choreics and the general population, and assuming the same frequency of Huntington's chorea among immigrants as in native-born, we note that 15 (17.9% $\pm$ 4.2%) of the male choreics are foreign-born, compared to 21.63 expected from the age-specific census distribution, and 12 (10.3%$\pm$2.8%) of the female choreics are foreign-born, compared to 27.45 expected. The proportion of foreign-born males is lower than expected, but not significantly so, while the proportion of foreign-born females is also lower than expected, being significantly different from expected at the 0.001 level. It seems likely that this deficiency of foreign-born choreics reflects a tendency of foreign-born carriers of the gene for Huntington's chorea either (a) not to migrate (before showing the trait), or (b) after migrating not to be recognized as choreics, rather than a lower frequency of chorea in these countries. Data to decide this point are not available.

The residence of choreics in 1940, classified as urban or rural, and Wayne County (which includes Detroit) or not, is presented in table 7. As indicated, the definitions of "urban" and "rural" are those of the U. S. Census for that year. Of the choreics, 73.5 per cent had an urban address, compared to 66.6 per cent for the general population; the difference is not significant. There is no significant difference between observed and expected proportion of choreics living in the Detroit metropolitan area (included in Wayne County).

Information is available for 109 white choreics who were age 20 or more on April

TABLE 7. RESIDENCE OF WHITE CHOREICS LIVING IN THE LOWER PENINSULA OF MICHIGAN ON APRIL 1, 1940. (RESIDENCE OF PERSONS IN INSTITUTIONS IS THE LAST NON-INSTITUTIONAL ADDRESS.)

Group	In Mental Institutions	Urban or rural				Wayne County (incl. Detroit)[4]
		Urban[1]	Rural-non-farm[2]	Rural-farm[3]	Total	
Males	Yes	17	1	2	20	10
	No	50	6	8	64	23
	Total	67	7	10	84	33
Females	Yes	21	2	4	27	11
	No	59	14	16	89	24
	Total	80	16	20	116	35
Total choreics	Number	147	23	30	200	68
	Proportion of total	0.735	0.115	0.150	1.000	0.340
Population, Lower Peninsula, 1940 Census		0.666*	0.170*	0.164*	1.000*	0.392†

1. Cities and incorporated places of 2,500 or more inhabitants.
2. Not on farms or in urban areas.
3. All persons living on farms, regardless of occupation.
4. Wayne County in 1940 was 95.7 percent urban by these definitions.

* All races. Population was 4,932,562 in 1940, 95.7 percent of whom were Caucasians.

† White only. Population was 1,850,437 in 1940.

1, 1940 on the number of years of education completed. For 88 such choreics information is lacking. Comparable data on education for non-choreic sibs were not obtained. These data are given in table 8, together with the expected numbers calculated from the 1940 census data for Michigan. If one considers only two educational groups, 0–6 years, and 7 or more years, and pools age groups (which do not differ significantly), it is found that the distribution of males differs significantly ($P < 0.01$) from expected, there being an excess in the 0–6 class, while females do not differ from expectation. Also, male choreics differ from female choreics ($P < 0.01$), there again being an excess of males in the 0–6 class. Since reliable educational data are available only for 55 per cent of the choreics, it is not clear how much significance to give these findings. It does appear that there is a sex difference in the amount of education received. Since this difference occurred before the onset of choreic movements, and, in many cases, before other signs of Huntington's chorea have appeared, the question arises whether this difference is due to some pre-choreic influence of the gene on its bearer or to social environment, which usually includes a choreic parent. Some children will have had to go to work early because their father was incapacitated by Huntington's chorea.

The distribution of "pre-choreic" occupations of choreics is of interest insofar as occupation is an indicator of social and intellectual competence. It is obvious that if significant differences are found they could be due to an early effect of the gene on its bearer or to the fact that a parent or other relative had Huntington's chorea.

TABLE 8. YEARS OF EDUCATION COMPLETED BY 109 WHITE CHOREICS IN THE LOWER PENINSULA OF MICHIGAN, AGE 20 YEARS OR MORE ON APRIL 1, 1940. (EXPECTED NUMBER, CALCULATED FROM 1940 CENSUS FOR MICHIGAN*, GIVEN IN PARENTHESES.)

Sex	Age	Years of education			Total	Education Unknown
		0–6	7–12	13 or More		
Males	20–44	6	11	1	18	13
		(1.7)	(14.2)	(2.1)	(18.0)	
	45 and over	11	14	0	25	26
		(8.5)	(14.9)	(1.6)	(25.0)	
	Total	17	25	1	43	39
		(8.4)	(30.4)	(4.2)	(43.0)	
Females	20–44	2	27	3	32	11
		(2.7)	(25.6)	(3.7)	(32.0)	
	45 and over	6	25	3	34	38
		(9.7)	(22.2)	(2.1)	(34.0)	
	Total	8	52	6	66	49
		(10.7)	(49.0)	(6.3)	(66.0)	
Males and females	20–44	8	38	4	50	24
		(4.5)	(39.6)	(5.9)	(50.0)	
	45 and over	17	39	3	59	64
		(18.4)	(36.8)	(3.8)	(59.0)	
	Total	25	77	7	109	88
		(19.5)	(79.0)	(10.5)	(109.0)	

* For all races, native and foreign-born.

Most studies have found that choreics appear to be members of the lower socio-economic levels of society. Panse (1942), for example, in his survey of the Rhineland, found 1.1 per cent of choreics were in the class of high officials and university teachers, while 21.3 per cent were unskilled laborers. The corresponding figures for his "comparison" kindreds (normal descendants of normal sibs of choreics) were 2.7 per cent and 13.4 per cent. These figures differ significantly for unskilled laborers. Panse did not have census data for comparison but data from several German studies also suggested that choreics and their normal sibs average lower on the social and occupational scale. The relevant comparison of occupations of choreics, their normal sibs, and the 1940 census, in the present study, is difficult for several reasons: (1) The "best" occupation of choreics seems most useful, since, as of 1940, most will be severely affected by the disease, but this occupation will occur at different times. (2) Decisions must sometimes be made as to which occupation is "best." (3) The normal sibs may not have their "best" occupation in 1940. (4) The major occupational groups of the 1940 census, used for classifying, are often internally heterogeneous. (5) For married women, the occupation of the 1940 husband must be used. For the comparison of occupations all sibships containing a choreic living on April 1, 1940 were used, but the choreic status of sibship members was taken as of the time of last investigation, i.e. at death or as of June 1956. Thus there are some choreics included who were "normal" on April 1, 1940. When a person had more than one major occupational group, the "best" one, according to the ranking shown in table 9, was used for tabulating. This ranking is unavoidably arbitrary.

TABLE 9. DISTRIBUTION OF "BEST"* OCCUPATIONS OF CHOREICS AND THEIR NON-CHOREIC SIBS. SIBSHIPS CONTAINING ONE OR MORE CHOREICS ON APRIL 1, 1940 IN MICHIGAN (LOWER PENINSULA PLUS FOUR UPPER PENINSULA SIBSHIPS). CHOREIC STATUS AS OF THE TIME OF LAST INVESTIGATION (DEATH OR JUNE 1956). NUMBERS IN PARENTHESES ARE NUMBERS OF PERSONS WITH TWO OR MORE OCCUPATIONS. PROPORTIONS ARE GIVEN BELOW THE NUMBERS AND ARE BASED ON TOTAL KNOWN.

Choreic Status	Major Occupational Group (1940 Census classification)									Total Known	Unknown	Total
	1	2	3	4	5	6	7	8	9			
Male												
Choreic	2 (0)	13 (7)	27 (4)	10 (2)	15 (6)	40 (8)	10 (3)	3 (1)	8 (0)	128	12‡	140
	.0156	.1016	.2109	.0781	.1172	.3125	.0781	.0234	.0625	0.9999		
Doubtfully choreic	1 (0)	0	2 (1)	0	1 (1)	2 (0)	1 (0)	1 (1)	2 (0)	10	2	12
	—		—		—	—	—	—	—	—		
Non-choreic	5 (1)	15 (2)	18 (0)	4 (2)	15 (3)	31 (3)	3 (0)	1 (0)	10 (0)	102	19	121
	.0490	.1471	.1765	.0392	.1471	.3039	.0294	.0098	.0980	1.0000		
Unknown	0	0	0	0	0	1 (0)	0	1 (0)	0	2	2	4
						—		—		—		
Proportion§ in Michigan	0.0584	0.1003	0.2066	0.1160	0.1117	0.2453	0.0580	0.0264	0.0772	0.9999	—	—
Female												
Choreic (married†)	3 (1)	13 (2)	30 (5)	6 (2)	26 (3)	15 (1)	4 (0)	2 (0)	18 (0)	117	40	157
	.0256	.1111	.2564	.0513	.2222	.1282	.0342	.0171	.1538	0.9999		
Choreic (single)	6 (3)	1 (0)	1 (1)	3 (1)	0	1 (0)	6 (0)	0	0	18	0	18
	.3333	.0556	.0556	.1667		.0556	.3333			1.0001		
Doubtfully choreic (married†, no single)	0	1 (0)	0	1 (0)	1 (0)	1 (0)	0	0	0	4	3	7
		—		—	—	—				—		
Non-choreic (married†)	2 (0)	11 (3)	9 (1)	5 (1)	11 (1)	16 (2)	1 (1)	0	4 (0)	59	51	110
	.0339	.1864	.1525	.0847	.1864	.2712	0.169		.0678	0.9998		
Non-choreic (single)	5 (2)	2 (0)	0	2 (0)	0	5 (0)	5 (0)	0	0	19	7	26
	.2632	.1053		.1053		.2632	.2632			1.0002		
Unknown (married†, no single)	0	0	0	1 (1)	0	0	0	0	0	1	1	2
				—						—		
Proportion§ in Michigan	0.1641	0.0505	0.0156	0.2992	0.0118	0.1665	0.2748	0.0043	0.0133	1.0001	—	—

Major occupational groups:

1. Professional and semi-professional workers.
2. Proprietors, managers, and officials, except farm.
3. Craftsmen, foremen, and kindred workers.
4. Clerical, sales, and kindred workers.
5. Farmers and farm managers.
6. Operatives and kindred workers (manual, usually routine, requiring little or no training).
7. Service workers (domestics, policemen, janitors, waitresses, etc.)
8. Farm laborers and foremen.
9. Laborers, except farm and mine.

* "Best" occupation as of time of last investigation. When a person had two or more major occupational groups over a period of time, the one with the lowest column number equivalent (i.e., 2 = proprietors, etc.) was chosen for tabulation.

† Occupation of *husband*.

‡ Includes one choreic who was "unemployed and seeking work."

§ Data from 1940 census for Michigan for persons 25 or more years of age with known occupation.

TABLE 10. POOLED DISTRIBUTION OF "BEST" OCCUPATIONS, CONDENSED FROM TABLE 9. NUMBER AND PROPORTION IN EACH CATEGORY.

Sex	Choreic status	Pooled major occupational groups* 1 + 2	3 + 4 + 5	6 + 7 + 8 + 9	Total
Males	Choreic	15	52	61	128
		0.1172	0.4062	0.4765	0.9999
	Non-choreic	20	37	45	102
		0.1961	0.3628	0.4411	1.0000
Married females	Choreic	16	62	39	117
		0.1367	0.5299	0.3333	0.9999
	Non-choreic	13	25	21	59
		0.2203	0.4236	0.3559	0.9998
Proportion of males in Michigan, 1940		0.1587	0.4343	0.4069	0.9999

* For married females, occupation of husband is used.

The distribution of "best" occupations is given in tables 9 and 10. Although table 9 contains too many categories for convenient use, it reveals that (a) choreic males and (b) husbands of choreic females are significantly deficient in professional and semi-professional workers (2-tailed probabilities less than 0.001 and 0.02, respectively) compared with the state of Michigan in 1940. On the other hand, the proportion of laborers does not differ significantly. Testing the distributions of grouped occupa-

TABLE 11. MARITAL STATUS ON APRIL 1, 1940 OF CHOREICS AND THEIR NON-CHOREIC SIBS LIVING IN MICHIGAN.* NUMBER FOR EACH CATEGORY. PERSONS WITH UNKNOWN MARITAL STATUS OMITTED (26). PROPORTION IN MICHIGAN FROM 1940 CENSUS.

Sex-Group-Institutional Status	Age 15–29 years					Age 30–44 Years					Age 45 or More Years				
	Single	Married	Divorced	Widowed	Total	Single	Married	Divorced	Widowed	Total	Single	Married	Divorced	Widowed	Total
Male choreic															
In	1	0	0	0	1	1	3	2	0	6	2	5	3	0	10
Out	3	2	0	0	5	5	12	3	0	20	7	24	3	4	38
Total	4	2	0	0	6	6	15	5	0	26	9	29	6	4	48
Female choreic															
In	0	0	0	0	0	1	4	1	1	6	2	12	4	6	24
Out	3	4	1	0	8	1	29	3	1	34	3	35	2	8	48
Total	3	4	1	0	8	2	33	4	1	40	5	47	6	14	72
Male non-choreic sibs	3	9	1	0	13	4	19	1	0	24	7	33	3	2	45
Female non-choreic sibs	4	9	0	0	13	2	22	1	0	25	9	33	1	5	48
Male-state population	.6975	.2969	.0044	.0012	—	.1545	.8124	.0211	.0120	—	.1092	.7616	.0242	.1049	—
Female-state population	.5241	.4627	.0095	.0038	—	.0882	.8492	.0287	.0340	—	.0651	.6626	.0198	.2525	—

* Lower Peninsula plus four Upper Peninsula sibships.

tions of table 10 shows that there are no significant differences between choreic males and non-choreic males or between males in the general population, similarly for husbands of choreic females. Pooling male choreics and husbands of female choreics to make a general class of choreics, (A), and male non-choreics and husbands of female non-choreics to make a class of non-choreics, (B), reveals no difference between Michigan males and A or B. However, A and B differ at the 0.05 level if occupations 1 and 2 are pooled to make one class and 3 through 9 another (but not for table 10 as it stands). All of these tests are selected out of a very large number of possible comparisons and their true significance is somewhat questionable. There is a definite suggestion, however, that choreics have a lower occupational status than their non-choreic sibs or the general population, possibly due more to a relative deficiency of "higher" occupations than to an excess of "lower" occupations. On the other hand, the choreics do not differ grossly from these two groups and the non-choreic sibs do not differ significantly from the general population. This absence of major differences is perhaps the clearest result.

The marital status of choreics and their non-choreic sibs on April 1, 1940 is presented in table 11 and the total number of marriages by that date is given in table 12. Table 11 illustrates the observed tendency of choreics to be divorced by their normal spouses before or during the time of institutionalization. Neither the choreics nor their non-choreic sibs differ significantly from the general population (comparisons being made within sexes). In the two higher age groups the proportion of single male choreics exceeds the corresponding proportion among female choreics and, if these two age groups are pooled, the proportions are found to differ at the 0.01 level of significance. It is interesting that Panse (1942) also found that the proportion of male choreics, age 30 or over, who were single (27.9% ± 2.9%) was significantly higher than the corresponding proportion for female choreics (17.8% ± 2.5%).

TABLE 12. NUMBER OF MARRIAGES BY APRIL 1, 1940 OF CHOREICS AND NON-CHOREIC SIBS. LOWER PENINSULA OF MICHIGAN PLUS FOUR UPPER PENINSULA SIBSHIPS.

Sex-Group-Institutional Status	15–29 Years of Age						30–44 Years of Age						45 or More Years of Age						
	Number				Total persons	Mean	Number				Total persons	Mean ± S.E.	Number					Total persons	Mean ± S.E.
	0	1	2	3			0	1	2	3			0	1	2	3	4		
Male choreic																			
In	1	0	0	0	1	0	1	3	2	0	6	1.17±0.31	2	9	1	0	0	12	0.92±0.15
Out	3	2	0	0	5	0.04	5	16	0	0	21	0.76±0.10	7	28	2	1	0	38	0.92±0.10
Total	4	2	0	0	6	0.33	6	19	2	0	27	0.85±0.10	9	37	3	1	0	50	0.92±0.08
Female choreic																			
In	0	0	0	0	0	0	1	5	0	0	6	0.83±0.17	2	17	4	2	0	25	1.24±0.14
Out	3	4	1	0	8	0.75	1	25	7	1	34	1.24±0.09	3	38	7	1	1	50	1.18±0.09
Total	3	4	1	0	8	0.75	2	30	7	1	40	1.18±0.09	5	55	11	3	1	75	1.20±0.08
Male non-choreic	3	10	0	0	13	0.77	4	19	2	0	25	0.92±0.10	7	37	3	0	0	47	0.91±0.07
Female non-choreic	4	9	0	0	13	0.69	2	22	1	0	25	0.96±0.07	9	38	6	0	0	53	0.94±0.07

TABLE 13. DISTRIBUTION OF INDIVIDUALS WHO HAD CHILDREN BORN OUT OF WEDLOCK. WHITE SIBSHIPS AT TIME OF LAST INVESTIGATION (DEATH OR JUNE 1956). LOWER PENINSULA OF MICHIGAN PLUS FOUR UPPER PENINSULA SIBSHIPS. INDIVIDUALS AGE 20 OR MORE WHO ARE TRACEABLE.

Sex	Choreic status	Number who had children born out of wedlock	Total number traceable
Male	Choreic	2	162
	Doubtfully choreic	0	15
	Non-choreic	1	155
	Unknown	0	9
Female	Choreic	8	197
	Doubtfully choreic	0	14
	Non-choreic	1	179
	Unknown	0	7

The non-choreic male sibs do not differ significantly from the non-choreic female sibs. None of the pooled age groups can be shown to differ from the general population. Inspection of table 12 reveals a definite tendency of female choreics, relative to other groups, to have several marriages. Confining attention to choreics who were not institutionalized on April 1, 1940 and comparing mean number of marriages, female choreics age 30–44 years are seen to differ significantly from male choreics ($P < 0.001$) and from female non-choreic sibs ($P < 0.02$) of the same age group. For the 45 and over age group, female choreics do not differ significantly from male choreics (but again have a higher mean number of marriages) yet still differ from female non-choreics ($P < 0.05$). Male choreics do not differ significantly from male non-choreics in these two age groups. Census data for this variable are not available. In order to interpret these findings properly a knowledge of the time of marriage in relation to the onset of Huntington's chorea is necessary, and this is not available. It is safe to assume, however, that almost all marriages take place before manifestation of choreiform movements has begun, though not necessarily before emotional or mental changes. The increased marriage rate observed in female choreics does appear to reflect an effect on its bearer of the gene for Huntington's chorea.

Table 13 gives the distribution, by choreic status, of individuals who have had children born out of wedlock. Male choreics do not differ from male non-choreic sibs or female non-choreic sibs, but female choreics differ significantly ($P < 0.05$, exact 2 x 2 test) from their female non-choreic sibs, 8 out of 197 having had an illegitimate child. This finding may well be a direct consequence of their chorea since, of the five whose ages at the time of onset of choreic movements are known, three had their illegitimate child after onset of choreic movements.

An attempt was made to compare criminal behavior of choreics and their non-choreic sibs. Through the kind cooperation of Commissioner Joseph A. Childs it was possible to check the files of the Michigan State Police for the names of sibship members and obtain details of crimes on record. For this comparison only sibship members, choreic and non-choreic, known to be living in Michigan on April 1, 1940, and also at the time of last investigation, were checked. The results are given in table 14. Five of 103 male choreics were recorded as having committed a serious crime, compared to none of 87 male non-choreics. These proportions differ signifi-

cantly at the 0.05 level. Three of 141 female choreics were similarly recorded, compared to none of 98 female non-choreics. These proportions do not differ significantly. For both sexes, two of the three individuals whose choreic status was known at the time of their "major" crime were choreic then (i.e. they had choreic movements). There may have been an increase in criminal activity of persons having the gene but not yet showing chorea, but these data do not prove it.

In reviewing these data on social and demographic characteristics of choreics and their normal sibs, perhaps the most noteworthy finding is that it was not possible to show that unaffected sibs differed from the general population with regard to occupational and marital status. These comparisons are not particularly suited for our purposes but it does appear that there are no marked differences. Thus, the distribution of occupations, for example, indicates that choreic kindreds, in the absence of Huntington's chorea, would not be clearly distinguished from the general population. It is difficult to believe, however, that the presence of affected individuals in a kindred for several generations would have no effect on the social behavior and economic status of unaffected members of the kindred. Our negative finding is contrary to that of most authors, but, of these, only Panse (1942) has made a large, comparative survey. It is not surprising that choreics are found to differ from non-choreic sibs and from the general population, but some of the differences between choreic males and choreic females are harder to explain. Any interpretation of differences between choreics and the general population is complicated by the facts that a given social action might reflect (a) the presence of the gene on its bearer or (b) the social environment created by choreic relatives. If due to (a) one can further inquire whether this effect may precede the physical symptoms of chorea. Since choreics and

TABLE 14. CRIMES COMMITTED BY SIBSHIP MEMBERS ON RECORD WITH MICHIGAN STATE POLICE. ONLY INDIVIDUALS LIVING IN MICHIGAN ON APRIL 1, 1940 AND ALSO AT TIME OF LAST INVESTIGATION (DEATH OR JUNE 1956).

	Choreic status at		Individuals having recorded crimes* Category				Individuals having no recorded crimes
Sex	Last investigation	Time of crime	1	2	3	Total	
Male	Choreic	Choreic	2	0	2	4	
		Non-choreic	0	1	2	3	94
		Unknown	1	1	0	2	
	Non-choreic	—	0	0	2	2	85
	Unknown	Unknown	0	0	2	2	10
Female	Choreic	Choreic	0	2	0	2	
		Non-choreic	0	1	0	1	138
		Unknown	0	0	0	0	
	Non-choreic	—	0	0	0	0	95
	Unknown	Unknown	0	0	0	0	5

* When an individual committed crimes in more than one category, the more serious category was tabulated.

Crime categories: 1. Murder, accomplice to murder, rape.
2. Breaking and entering, larceny, false pretenses, soliciting for prostitution.
3. Drunkeness, illegal possession of liquor, traffic violations, other minor charges.

their non-choreic sibs have had relatively similar early social environments, those traits for which choreics differ from the general population, and non-choreics do not, can be said to be due to possibility (a). This is the case for occupation. It is not possible to state what proportions of the differences found are due to mental and emotional changes before onset of chorea. The "best" major occupational group and the ultimate marital status, in many cases, have been determined by the age at which chorea usually develops, but certainly not in all cases. After onset of chorea, of course, it is hardly remarkable that differences should be found. The data on illegitimacy and criminality appear to demonstrate differences of this sort. It therefore seems difficult and perhaps unjustified, to go beyond the obvious conclusion that overt chorea affects social and intellectual behavior.

PROGRESS OF THE DISEASE

Although the present study is not primarily concerned with the clinical aspects of Huntington's chorea, certain data on the characteristics of the disease are necessary to the arguments to be developed later in this and a paper to be published. Objective data on three landmarks in the progress of the disease, *onset*, *institutionalization*, and *death*, are available and will be considered in this section. Data on suicide and cause of death will also be presented.

The age at onset is the most important statistic to be considered and it is necessary to emphasize some unavoidable deficiencies in this variable. We are concerned here with the onset of choreiform movements, not of mental or emotional changes, since this is the only aspect for which reasonably objective data, for both institutionalized and uninstitutionalized individuals, can be obtained. In any individual instance, however, the age at onset may be in error by several years, since discrepancies of this order between reports of equally reliable observers, close to the choreic concerned, are quite common. When the reports differed by more than several years the age was considered to be unknown, and for some persons it was not possible to obtain any

TABLE 15. AGE AT ONSET OF CHOREIC MOVEMENTS. STATUS AT TIME OF LAST INVESTIGATION (DEATH OR JUNE 1956). INDIVIDUALS WITH KNOWN AGE OF ONSET IN SIBSHIPS CONTAINING A MICHIGAN CHOREIC ON APRIL 1, 1940.

Sex	Living or Dead	Age at Onset										Total	Mean	Standard Deviation	Standard Error
		15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69				
Male	Living	2	2	2	5	8	2	2	0	0	0	0	23	33.70	8.36	1.74
	Dead	4	7	9	9	13	10	6	4	0	0	1	63	34.86	10.28	1.30
	Total	6	9	11	14	21	12	8	4	0	0	1	86	34.55	9.77	1.05
Female	Living	1	5	1	6	3	6	2	2	0	0	1	27	35.93	11.79	2.27
	Dead	5	8	8	15	18	21	12	4	0	0	0	91	35.82	9.24	0.97
	Total	6	13	9	21	21	27	14	6	0	0	1	118	35.85	9.83	0.90
Male and Female	Living	3	7	3	11	11	8	4	2	0	0	1	50	34.90	10.32	1.46
	Dead	9	15	17	24	31	31	18	8	0	0	1	154	35.43	9.66	0.78
	Total	12	22	20	35	42	39	22	10	0	0	2	204	35.30	9.80	0.69

information on onset. Other workers have also remarked on the difficulties of determining the age at onset.

All data on the progress of the disease pertain to the choreic members of sibships which, on April 1, 1940, contained one or more choreic individuals living in Michigan. Where applicable, e.g., for age at death, data on these individuals as of the time of last investigation is used. This procedure will make the data more homogeneous in time than they would be if other sibships and generations were used; for variables such as age at institutionalization and age at death, such homogeneity is clearly desirable. It is believed that the onset data are also improved. This restriction in time introduces some bias, since there is selection for a long onset-death interval in the sibship propositus, but this seems less serious than the disadvantage of data covering a wider time span. The choreic sibs of the 1940 propositus, of course, are not selected for long onset-death interval.

In table 15 the distribution of age at onset in 204 choreics is presented. None of the divisions by sex or by whether living or dead differ significantly in mean or variance so that the value for the total distribution may be used, the mean being 35.30 ± 0.69 years, standard deviation 9.80 years. This mean agrees closely with that found in other large studies, e.g. Panse (1942): 36.19 years; Bell (1934): 35.51 years. The standard deviation is significantly (at the 0.001 level) smaller however. In the two studies above, it was 12.3 and 12.38 years, respectively. In keeping with the smaller standard deviation of the present study, the range of ages is less, being 15 to 65, while both Panse (446 cases) and Bell (460 cases) report individuals in the 0–4 and the 70–74 age groups. In comparing these studies it is necessary to remember that Panse's data cover several generations, including persons long-deceased and Bell's are compiled from the literature and are therefore somewhat selected. It is not clear how real this difference in standard deviation is.

The distribution of the age at first institutionalization (because of Huntington's chorea) is presented in table 16. The mean for 89 males is 48.11 ± 1.22 years; for 103 females it is 48.87 ± 1.13 years. There appear to be no data, for a specified area, for comparison and, in fact, this variable, by itself, is too much a function of local hospital facilities and social customs to be valuable for comparisons.

TABLE 16. AGE AT FIRST INSTITUTIONALIZATION. STATUS AT TIME OF LAST INVESTIGATION (DEATH OR JUNE 1956). INDIVIDUALS EVER INSTITUTIONALIZED IN SIBSHIPS CONTAINING A MICHIGAN CHOREIC ON APRIL 1, 1940.

Sex	Living or Dead	Age at First Institutionalization											Total	Mean	Standard Deviation	Standard Error
		20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79				
Male	Living	0	0	1	4	4	2	1	2	1	0	0	1	16	46.38	11.59	2.90
	Dead	0	3	5	10	11	10	9	12	5	7	0	1	73	48.49	11.51	1.35
	Total	0	3	6	14	15	12	10	14	6	7	0	2	89	48.11	11.48	1.22
Female	Living	0	0	1	5	3	5	4	3	1	3	0	1	26	49.92	11.76	2.31
	Dead	1	1	6	8	16	11	12	5	10	4	2	1	77	48.52	11.40	1.30
	Total	1	1	7	13	19	16	16	8	11	7	2	2	103	48.87	11.45	1.13

TABLE 17. AGE AT DEATH OF CHOREIC INDIVIDUALS. INDIVIDUALS IN SIBSHIPS CONTAINING A MICHIGAN CHOREIC ON APRIL 1, 1940. S.D. = STANDARD DEVIATION, S.E. = STANDARD ERROR.

Sex	Age at death																
	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85–89	Total	Mean	S.D.	S.E.
Male	1	2	4	12	14	15	23	12	16	12	8	5	1	0	125	53.05	12.65	1.13
Female	1	2	5	8	10	23	25	17	18	13	9	5	0	1	137	54.11	12.29	1.05

The age of choreics at death has been studied by a number of workers. In table 17 the distribution of these ages for 125 males and 137 females is given. The respective means of 53.05 ± 1.13 and 54.11 ± 1.05 years are strikingly close to those reported by Bell (1934) and Panse (1942). The former gives 53.55 ± 0.63 and 52.59 ± 0.74 years and the latter 52.24 ± 0.76 and 52.15 ± 0.69 years, respectively. The deaths in the present study include eight "unnatural" deaths (accidents and suicides) among males and five among females. For comparison, the age at death in 1940 for whites of the death-registration states of the U. S. was 62.1 years for males and 66.6 years for females (Vital Statistics—Special Reports, Vol. 33—U. S. Public Health Service). The absence of a significant sex difference is not surprising if the chorea is a fairly direct cause of death, overriding to an appreciable extent other causes of death. The definite effect of the disease on life span is seen more clearly in the distribution of the onset-death interval given below.

The distribution of the interval between onset and first institutionalization, for 49 males and 69 females, is given in table 18. The mean for males is 10.59 ± 0.96 years and for females, 12.67 ± 0.98 years. These means do not differ significantly. Since the propositus for each kindred is ascertained after he has come to medical attention, the distribution in table 18 indicates that any survey of choreics is likely to miss a certain proportion of affected individuals. This proportion should be small in the present study since kindreds were ascertained through all known choreics in Michigan, including long-deceased individuals, but if a 1940 kindred were represented by only one living Michigan choreic, and by no deceased Michigan choreics, a long onset-institutionalization interval could lead to non-ascertainment.

The interval between onset and death is a good indicator of the progress of the disease. The distribution of this variable for 65 males and 88 females is given in table 19. The mean for males is 15.78 ± 1.00 years; for females it is 15.93 ± 0.91 years. The corresponding figures found by Bell (1934) are 13.72 years (sexes pooled)

TABLE 18. INTERVAL BETWEEN ONSET AND FIRST INSTITUTIONALIZATION OF CHOREIC INDIVIDUALS. INSTITUTIONALIZED INDIVIDUALS IN SIBSHIPS CONTAINING A MICHIGAN CHOREIC ON APRIL 1, 1940.

Sex	(Year of First Institutionalization)—(Year of Onset)								Total	Mean	Standard Deviation	Standard Error
	0–4	5–9	10–14	15–19	20–24	25–29	30–34	48				
Male	9	14	13	8	3	1	1	0	49	10.59	6.75	0.96
Female	10	19	13	12	12	1	1	1	69	12.67	8.16	0.98

TABLE 19. INTERVAL BETWEEN ONSET AND DEATH OF CHOREIC INDIVIDUAL. INDIVIDUALS IN SIBSHIP CONTAINING A MICHIGAN CHOREIC ON APRIL 1, 1940.

Sex	Age of Onset	(Year of Death)—(Year of Onset)										Total	Mean	Standard Deviation	Standard Error	Average Future Life-time—U.S. White Population, 1940*
		0–4	5–9	10–14	15–19	20–24	25–29	30–34	36	45	51					
Males	15–19	0	0	1	3	0	0	0	0	0	0	4	15.25	2.06	1.03	50.5
	20–24	1	1	4	0	0	0	1	0	0	0	7	15.57	9.18	3.47	46.0
	25–29	0	1	2	4	1	0	0	1	1	0	10	20.20	11.87	3.75	41.5
	30–34	1	1	2	5	1	1	0	0	0	0	11	15.00	7.18	2.17	37.0
	35–39	2	0	2	7	0	0	2	0	0	0	13	15.77	9.07	2.51	32.6
	40–44	0	1	4	3	1	1	0	0	0	0	10	15.60	5.93	1.87	28.3
	45–49	1	2	0	3	0	0	0	0	0	0	6	11.83	7.20	2.94	24.3
	50–54	0	0	3	1	0	0	0	0	0	0	4	14.25	2.06	1.03	20.5
	Total	5	6	18	26	3	2	3	1	1	0	65	15.78	8.09	1.00	—
Females	15–19	0	0	1	1	2	0	0	0	0	1	5	24.60	15.74	7.04	54.2
	20–24	1	1	2	0	1	0	1	0	0	0	6	14.50	11.11	4.54	49.5
	25–29	0	1	1	0	3	3	0	0	0	0	8	20.50	6.72	2.38	45.0
	30–34	1	3	2	6	3	0	0	0	0	0	15	13.87	6.32	1.63	40.4
	35–39	0	3	5	6	1	1	2	0	0	0	18	16.61	7.43	1.75	35.9
	40–44	1	5	4	5	1	3	0	0	0	0	19	14.32	7.81	1.79	31.5
	45–49	1	0	5	3	1	1	1	0	0	0	12	16.33	8.72	2.52	27.2
	50–54	1	0	1	2	0	0	0	0	0	0	4	11.75	7.27	3.64	23.1
	55–59	0	0	0	0	0	0	0	0	0	0	0	—	—	—	19.2
	60–64	0	0	0	0	0	0	0	0	0	0	0	—	—	—	15.6
	65+	0	1	0	0	0	0	0	0	0	0	1	6.00	—	—	—
	Total	5	14	21	23	12	8	4	0	0	1	88	15.93	8.55	0.91	—

* Years of life remaining for normal individuals in indicated group. Data for mid-age of the five year interval, e.g., 17, 22, etc. (Vital Statistics—Special Reports, U. S. Bureau of the Census, 1945).

and by Panse (1942) 13.87 ± 0.62 and 13.05 ± 0.48 years. The present data agree with those of Bell in not finding a clear effect of age of onset on the interval between onset and death. Comparison in table 19 of the onset-death intervals with the expected future survival in normal individuals reveals a definite shortening of life in the choreics, especially among those with early onset.

An increased rate of suicide among choreics has been noted by many authors and the data of table 20 also show this tendency, the frequency among non-institutionalized male choreics being significantly elevated relative to male non-choreics and similarly for females. Suicide was an important cause of death among the non-institutionalized choreic population, accounting for 7.8 per cent of deaths in males and 6.4 per cent in females (sibship data).

Cause of death is often difficult to assign and, when several contributing factors occur together, is often difficult to interpret, but it may still be of interest to list some major categories of causes of death of choreics who died after April 1, 1940. Table 21 presents these data for 13 deaths under age 40 and 148 deaths at age 40 or over. Aside from Huntington's chorea, heart disease and pneumonia are most frequently listed among the causes of death. The former cause is not unusual in any population mostly over age 40 but the latter seems to be a more particular complica-

TABLE 20. DISTRIBUTION OF SUICIDES AMONG INDIVIDUALS IN SIBSHIPS CONTAINING A MICHIGAN CHOREIC ON APRIL 1, 1940. ONLY INDIVIDUALS SURVIVING TO AGE 15 OR OLDER. THREE INDIVIDUALS REPORTED NORMAL BUT HAVING CHILDREN WITH MEDICALLY DIAGNOSED HUNTINGTON'S CHOREA ARE OMITTED. STATUS AT TIME OF LAST INVESTIGATION.

Individuals	In Mental Institution	Total Number of Individuals	Number of Suicides	Proportion of Individuals Committing Suicide	Range of Ages ot Time of Suicide
Male choreics	Yes	91	0	—	
	No	77	6	0.078	37–50
	Total	168	6	0.036	
Female choreics	Yes	105	0	—	
	No	94	6	0.064	30–78
	Total	199	6	0.030	
Male non-choreics		161	2	0.012	39–42
Female non-choreics		181	1	0.006	39

TABLE 21. CAUSE OF DEATH OF WHITE CHOREICS ALIVE IN MICHIGAN ON APRIL 1, 1940. DATA FROM MEDICAL RECORDS, EXCEPT CONCERNING ACCIDENTS AND SUICIDES. "H. C." = HUNTINGTON'S CHOREA

Recorded Cause	Age at Death: Under 40	Age at Death: 40 or over
H. C. only	4	14
H. C. and one or more other diseases	2	42
No H. C. but one or more other diseases	2	42
Accident or suicide	2	1
Not given	3	49
Total	13	148
Causes below counted irrespective of other concomitant diseases:		
Heart disease, any form	0	23
Pneumonia, any form	3	22
Exhaustion, debility or senility	0	6

tion of chorea, largely in consequence of the terminal debility and the aspiration of food into the lungs. Perhaps the most striking fact is that of five choreics dying under 40 whose cause of death is reported and is not due solely to Huntington's chorea, accident, or suicide, three are reported to have had pneumonia. The suicide rate among this group of choreics is lower than that discussed above, largely because these choreics are selected for having been alive on April 1, 1940.

In reviewing these various measures of the progress of this disease, two main findings appear. Thus, in spite of the definitely chronic and progressive nature of Huntington's chorea, there is great individual variability in the onset and rate of progression of the disease as measured by ages at onset, institutionalization, and death. The other general finding is that there is no significant sex difference in these quantities, a result differing from some of those of the preceding section.

GENETICS OF HUNTINGTON'S CHOREA

The dominant inheritance of Huntington's chorea is apparent in all family studies and is accepted by all investigators, subject only to qualifications due to late onset and difficulties of diagnosis. Critical analysis of the segregation ratio among children of choreics, however, appears to have been done only by Sjögren (1935) and Panse (1942). Both found a satisfactory approach to a 1:1 ratio when a proper minimum age for classifying the children was adopted. In table 22 the proportion of choreic children in sibship data of the present study is given. Proportions for several different minimum ages were calculated because it is not obvious which age is best. One wishes to correct for both late onset and early death. As the table shows, satisfactory agreement is found for minimum ages 30 through 50 years. Family pedigrees show that the gene for Huntington's chorea is clearly autosomal in inheritance and the proportion of males among choreics in the sibships studied above agrees with this finding. For minimum ages 30, 40, 50, and 60 years, the proportions are 0.488, 0.476, 0.486, and 0.500, respectively, none of these differing significantly from 0.5. For this reason it is difficult to see how the significant deficiency of choreic males living in Michigan on April 1, 1940, found earlier, arose. Since other surveys have not found a deficiency it appears that this is only a chance finding, not likely to be repeated.

In table 23 the distribution is given of the number of known affected generations in kindreds containing a Michigan choreic on April 1, 1940. The data were usually

TABLE 22. PROPORTION OF CHOREICS AMONG CHILDREN OF CHOREICS. WHITE INDIVIDUALS IN SIBSHIPS CONTAINING A MICHIGAN CHOREIC ON APRIL 1, 1940. SIBSHIPS WITH MORE THAN TWO DOUBTFULLY CHOREIC INDIVIDUALS ARE OMITTED. METHOD OF HALDANE (1938) IS USED AND COMPLETE ASCERTAINMENT IS ASSUMED.

Treatment of Dubious Choreics	Minimum Age o Classified Children			
	30 years	40 years	50 years	60 years
Considered choreic	0.529 ± 0.025	0.525 ± 0.027	0.486 ± 0.034	0.355 ± 0.049
Considered normal	0.484 ± 0.025	0.482*	0.450*	0.311*

* The standard error is very nearly that given directly above.

TABLE 23. NUMBER OF GENERATIONS AFFECTED WITH HUNTINGTON'S CHOREA. KINDREDS CONTAINING A WHITE MICHIGAN CHOREIC ON APRIL 1, 1940. LAY REPORTS OF CHOREA ACCEPTED.

No. of Choreic Individuals in Kindred on April 1, 1940	No. of Generations in Kindred Reported Affected							Total	Mean
	1	2	3	4	5	6	7		
1	21	23	16	3	5	1	0	69	2.29
2	2	9	10	10	3	0	1	35	3.20
3	1	2	3	2	2	1	0	11	3.45
4	0	0	1	1	2	0	0	4	4.25
5	0	0	0	2	1	0	0	3	4.33
6	0	1	0	0	1	0	0	2	3.50
Total	24	35	30	18	14	2	1	124	2.78

obtained from reasonably reliable informants instead of from medical sources. Those kindreds with only one or two affected generations known, almost always represent kindreds where no or little family investigation was possible or where one or more ancestors died relatively young. A critical discussion of kindreds with only one affected generation known and where both parents lived to age 60 or over, thus suggesting the occurrence of mutation, will be presented in the second part of this study. However, it is obvious from the table that new mutation accounts for only a small proportion of the observed cases of Huntington's chorea and that extensive pedigrees of affected individuals are common. Thus, 35 (out of 124) kindreds were studied in which, with reasonable reliability, four to seven affected generations were reported. These observations are in striking contrast to findings in the majority of well-studied rare dominant traits in man, such as achondroplasia (Mørch, 1941) or neurofibromatosis (Crowe, Schull, and Neel, 1955).

The heritability, i.e. degree of genetic determination, of (1) the age at onset of chorea, (2) age at death from chorea, and (3) interval between onset and death (measuring rate of progression) can be estimated from the sibship data. Analysis of variance, comparing variation within and between sibships, is the most convenient method of testing for such determinations and this analysis is presented in table 24. The most sensitive between-within sibships comparison uses the mean square for "between sibships, between kindreds"; i.e. it does not use the variation between

TABLE 24. ANALYSIS OF VARIANCE OF AGE OF ONSET, AGE AT DEATH, AND INTERVAL BETWEEN ONSET AND DEATH. SIBSHIPS CONTAINING A MICHIGAN CHOREIC ON APRIL 1, 1940.

Variable	Source	S.S.	D.F.	M.S.	F	P
Age at onset	Between sibships, between kindreds	11,468.13	99	115.840	1.623	.05 > P > .01
	Between sibships, within kindreds	2,735.74	25	109.430	1.533	>.05
	Between sibships, total	14,203.87	124	114.547	1.604	.05 > P > .01
	Within sibships	5,710.22	80	71.378		
	Total	19,914.09	204	97.618		
Age at death	Between sibships, between kindreds	23,082.16	112	206.091	2.532	<.001
	Between sibships, within kindreds	5,147.09	30	171.570	2.107	<.01
	Between sibships, total	28,229.25	142	198.798	2.442	<.001
	Within sibships	8,710.84	107	81.410		
	Total	36,940.09	249	148.354		
(Age at death) minus (Age of onset)	Between sibships, between kindreds	5,171.36	85	60.840	1.196	>.05
	Between sibships, within kindreds	1,564.02	16	97.751	1.922	.05 > P > .01
	Between sibships, total	6,735.38	101	66.687	1.311	>.05
	Within sibships	2,085.43	41	50.864		
	Total	8,820.81	142	62.118		

sibships within the same kindred. A further comparison, testing whether there is a kindred resemblance apart from sibship resemblance, is possible if the ratio of mean squares of the two components of "between sibships" is obtained. None of these latter ratios is significant however. For onset and for death the variance between sibships is significantly larger than within sibships but this is not clearly the case for the onset-death interval. For this interval, however, the variance between sibships does exceed that within sibships. It seems reasonable to interpret the greater similarity among sibs in age at onset and at death as a consequence of their greater genetic similarity. Whether this increased similarity is due primarily to (a) the possession in common of similar "background" genes against which a gene for Huntington's chorea manifests itself, Huntington's chorea being due almost entirely, or exclusively, to one particular gene, or to (b) the possession in common of the same particular gene for Huntington's chorea, the same clinical appearance of Huntington's chorea being produced by any one of several different genes, at one or more loci, having frequencies which do not differ greatly, cannot be definitely decided from this analysis. Possibility (a) seems more likely, however, because the "between sibships, within kindreds" mean square exceeds the "within sibships" mean square for all three variables. A given "background" of two or more genes, present in one choreic, is more likely to be found in his sib than in a more distant relative, while the same allele producing chorea should be present throughout the kindred.

In other studies the similarity between sibs has more often been tested by finding the intra-class correlation coefficient and testing whether it differs significantly from zero. Fieller and Smith (1951) have given reasons for preferring the analysis of variance to the latter procedure. They also give formulas for deriving an improved estimate of the correlation coefficient from the components of variance. Using their procedure, the sib-sib coefficients for onset and for death are 0.28 and 0.47, respectively, and these are already known to be significantly different from zero. Bell (1934), using data from the literature, calculated a sib-sib correlation coefficient of 0.64. She discusses the possibility of bias due to utilizing incomplete histories in which sibs who may become choreic later are counted as normal. This bias would spuriously increase the correlation. Also, in the product-moment method, the large sibships are unduly weighted with respect to the smaller sibships (cf. Fieller and Smith, 1951), another source of bias. The sibships used in the present study were ascertained as of 1940 and followed until 1956, so that the first source of bias should be small, while deriving the estimate from the variances should minimize the second. It is therefore not too surprising that the two estimates differ appreciably. The higher correlation of age at death agrees with a general impression that in some kindreds there is marked similarity in the age at death from chorea, especially when at low ages. The correlation in age at death between normal sibs may also account for the higher value. Beeton and Pearson (1899) found a significant correlation, 0.26, between brothers in age at death.

The frequency in Michigan of individuals heterozygous for the gene determining Huntington's chorea, as distinguished from persons recognized as choreics, is of interest and can be approximately estimated. Since heterozygotes cannot be identified before onset, all methods of estimation must be indirect and each has certain

biases. In this situation the following approach seems as good as any. If H is the number of observed Huntington's choreics in an area at time t, P_x is the proportion of heterozygotes whose chorea is recognized by age x, N_x is the total number of individuals in the area at time t who are age x, and f is the frequency of heterozygotes in the general population in this area at time t, then

$$f = \frac{H}{\sum_x N_x P_x}$$

summing over all ages. We have determined H for the Lower Peninsula of Michigan in 1940 (203 individuals) and the N_x's for this area and time are known from the census of that year. P_x can be approximated from the observed age at onset curve, using the grand total distribution in table 15. This distribution, with mean 35.30 years and standard deviation 9.80 years, agrees closely with the corresponding normal distribution ($\chi^2_7 = 7.32$) so that values for P_x can be estimated from the normal curve. These values are slightly low because of the heterozygotes who are omitted from the onset data, due to failure to develop chorea by the time of the survey, either because of death or, if living, because the age at onset had not been reached. The segregation proportions show that this bias is small. Using the above-discussed values, the frequency of heterozygotes is estimated as 1.01×10^{-4} or one in 9,900 individuals. The gene frequency, of course, is half this value. The estimate of f is for the whole population and, because of mortality due to Huntington's chorea, the age-specific values will be somewhat higher for lower ages than high ones. Since the frequency of recognized choreics is estimated to be 4.12×10^{-5}, this means that only about 40 per cent of heterozygotes were identified as such. Because both numerator and denominator in the estimate are probably underestimates, the direction of probable bias of this estimate is unknown. The magnitude of the bias is also unknown but it seems unlikely to exceed about 10 per cent since the biases of numerator and denominator tend to cancel each other.

SUMMARY

In a study undertaken primarily to obtain data on natural selection and mutation in Huntington's chorea (to be analyzed in a following paper) the Lower Peninsula of the state of Michigan, U. S. A., was surveyed in 1954–1956 in an attempt to locate and investigate all individuals in this area, living or dead, ever institutionalized or not, who have developed this disease. A count of such persons as of April 1, 1940 yielded 203 individuals in 124 kindreds (groups of biologically related individuals). The population of this area in 1940 was 4,932,562, giving a frequency of choreics of 4.12×10^{-5} or about 1 in 24,000 individuals. The frequency of individuals heterozygous for the dominant gene for Huntington's chorea is estimated as 1.01×10^{-4}.

Certain demographic and social characteristics of choreics were compared with those of their normal sibs. When possible additional comparisons were made with the 1940 U. S Census. There were no marked differences between the non-choreic sibs and the population of the State of Michigan with respect to occupation and marital status. Choreics appeared to differ from their normal sibs and from the population of Michigan in a number of respects.

The dominant inheritance of the disease was confirmed. Data on the progress of the disease, as indicated by age at onset, institutionalization, and death, and the intervals between these ages, were obtained. Among sibs the ages at onset and the ages at death are significantly correlated, the correlation coefficients being 0.28 and 0.47. The sib-sib correlation for the rate of progress of the disease, as shown by the onset-death interval, is not significantly different from zero. Analysis of variance suggests that the sib-sib correlations are probably due to similar genetic backgrounds rather than to the possession in common of the same particular gene for Huntington's chorea, if several such genes, at one or more loci, do in fact exist.

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